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10/589,143	08/14/2006	Ekaterina Igorevna Dementieva	U 016440-6	6787

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EXAMINER	
HINES, JANA A	
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1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,143	DEMENTIEVA ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-9 are under consideration in this office action.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on August 14, 2006 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

4. Claims 1-9 are objected to because of the following informalities:

a) Claim 1 appears to be missing words and has incomplete statements. For instance see steps 1(b) and 1(d). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 2-3 recite alternative limitations which are improperly expressed. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group recites members as being "selected from the group consisting of A, B and C". Another acceptable form recites "selected from 1, 2, 3, or 4." Applicant may correct this by amending the claim to recite the appropriate language.

b) Claim 1 refers to various bacterial, plant or animal toxins and biotoxins. However claim 3 is drawn to biotoxins comprising staphylococcal entertoxin B, diphtheria and anthrax toxin. However staphylococcal entertoxin B, diphtheria and anthrax toxin are bacterial and would likely be classified as bacterial toxins. It is noted that the terms "biotoxins" and "toxins" are used as equivalents by the claims. However it is requested that consistent terminology be used throughout the claims.

c) Claim 3 recites "immobilized biotoxins" however it is unclear where the immobilized biotoxins came from and there is insufficient antecedent basis for the phrase. Therefore appropriate correction is required to overcome the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al., (US Patent 6,630,358 published October 2003) in view of Ewalt et al., (2001. Analytical Biochem. Vol. 289:162-172).

The claims are drawn to method for quantitative detection of biotoxins in a sample, comprising the steps of: *a)* manufacturing a biological microchip comprising .an ordered array of three-dimensional hydrogel elements on a solid support, obtained by a method of photo- or chemically induced polymerization and containing immobilized antibodies to various bacterial, plant or animal toxins or biotoxins, wherein an antibody to an individual biotoxin or an individual biotoxin is immobilized in each separate cell; *b)* incubating the microchip in a reaction medium which comprises a sample containing biotoxins to be analyzed, for forming immune biotoxin-antibody complexes, which incubation, when necessary, is carried out under stirring conditions; *c)* detecting the formed complex; and *d)* quantitative detection of the biotoxin being analyzed. Claim 2 is drawn to the immobilized antibodies comprising antibodies selected from the group of antibodies to ricin, viscumin, staphylococcal enterotoxin B, tetanus toxin, diphtheria toxin, lethal factor of anthrax toxin. Claim 3 is drawn to the immobilized biotoxins

comprising biotoxins selected from the group comprising ricin, viscumin, staphylococcal enterotoxin B, tetanus toxin, diphtheria toxin, lethal factor of anthrax toxin. Claim 4 is drawn to detecting the complex formed in step *c)* and subsequent quantitative detection in step *d) are* carried out in a format of direct immunoassay.

Claim 5 is drawn to the reaction medium in step; *b)* additionally contains antibodies to a biotoxin, and the detection of the complex formed between the biotoxin immobilized on the chip and the antibody against this biotoxin in step; *c)* and subsequent quantitative detection in step *d) are* carried out in the format of competitive immunoassay. Claim 6 is drawn to the reaction medium in step *b)* further contains a labeled biotoxin, and detection of the complex formed between the antibody immobilized on the chip and the biotoxin in step *c)* and subsequent quantitative detection in step *d) are* carried out in the format of competitive immunoassay. Claim 7 is drawn to detection of the complex formed in step *c)* and subsequent quantitative detection in step *d) are* carried out in the format of sandwich-immunoassay. Claim 8 is drawn to the quantitative detection of the biotoxin is effected by carrying out steps *a)--c)* with known concentrations of the biotoxin being analyzed and with plotting a calibration dependence curve, from which the amount of the biotoxin being analyzed in the sample is determined. Claim 9 is drawn to the step *c)* wherein detection of the formed complex is carried out fluorimetrically, chemiluminometrically or mass-spectrometrically.

Wagner et al., teach a variety of protein arrays, method and protein-coated substrates useful for clinical diagnostics (col. 4, lines 37-40). Wagner et al., teaches protein or antigen capture agents as being a molecule or multi-molecule complex which

binds the protein wherein antibodies are suitable as capture agents (col. 5-6, lines 60-10). Wagner et al., teach arrays of protein comprising microscale patterns of patches of protein immobilized on an organic thinfilm coating on the surface of the substrate (col. 8, lines 27-33). Wagner et al., teach coating a thin organic layer onto the surface wherein hydrogel comprises the thin organic layer (col. 6, lines 61-66 and col. 7, lines 33-35). Wagner et al., teach an array in an arrangement that is three-dimensional (col. 6, lines 41-45). Wagner et al., teach micromachining and micro fabrication refers to the techniques useful to the generation of array structures wherein the technologies include electrodeposition, physical and chemical etching, photolithography, polymerization and other well known techniques (col. 6, lines 50-60, col. 12, lines 54-59).

Wagner et al., teach affinity tags as moiety capable of directly or indirectly immobilizing a protein onto the functionality of the organic thinfilm which enhances the orientation of the protein onto the organic thinfilm (col. 9, lines 9-15). Wagner et al., teach a plurality of different proteins present of the array (col. 9-10, lines 62-8). Wagner et al., teach delivering the sample to a protein array comprising proteins that are detected either directly or indirectly (col. 28, lines 1-7). Wagner et al., teach using the array with a plurality of analytes being assed which are indicative of a pathogen or drug (col. 29, lines 20-27). Examples 9 and 10 teach incubation of the microchip/array in a reaction mixture under shaking/stirring conditions. Wagner et al., teach a wide range of detection methods include quantitative or qualitative detection, chemiluminescence, fluorescence and other well known methods (col. 26, lines 17-45). Wagner et al., teach detection methods for traditional immunoassays, noncompetitive, competitive, dual

labels, and radiometric immunoassays (col. 26, lines 45-53). However Wagner et al., do not specifically recite detecting biotoxins.

Ewalt et al., teach detection of biological toxins on a microchip. Ewalt et al., teach an array of capture antibodies is created by placing the specific labeled antibody on the chip at the desired microlocation (Figure1). The antibody is immobilized, a sample containing the protein to be assayed is placed on the chip, the protein analyte (fluroscein labeled SEB or cholera) is attracted; the proteins are specifically bound to their capture antibody at the microlocation and are measured directly by fluorescence detection from the top surface of the chip (Figure 1). Ewalt et al, teach a toxin-specific array which provided shortened assay time and increased sensitivity (page 168, col.1). Ewalt et al., teach detection of toxins from a mixture and teach that the chip integrates multiple assays locations in an array format for simultaneous detection of multiple analytes (page 169, col. 1). Ewalt et al, teach the permeation layer serves to immobilize any labeled capture antibodies and distance the assay site containing the labeled antibodies (page 170, col.1). Ewalt et al., teach microchip applications are advantageous because the assay large numbers of samples in a matter of minutes and microchip technology works with immunoassays and in combination with mass spectrometry (page 162). Ewalt et al., teach microchip technologies have application in the diagnostic detection of many biomolecules including biological warfare (page 162, col.2). Ewalt et al., detected labeled biological toxins staphylococcal entertoxinB (SEB) and cholera toxin as part of a platform for detecting warfare agents (page 163, col.1). Ewalt et al., teach the preparation of capture antibodies and toxins, including label

antibodies, antibodies against SEB and cholera (page 163, col.1). Ewalt et al., teach chips having an agarose permeation layer that coats the surface and an array with 25 sites wherein the array immobilized capture antibodies at multiple sites (page 163). Ewalt et al., teach labeled capture antibodies, toxins including fluorescein labeled SEB, incubation of the chip after receiving sample and measuring fluorescence and comparing the pattern of fluorescein fluorescence on the chip (page 164).

Therefore it would have been prima facie obvious at the time of applicants invention to modify the method for quantitative detection comprising: *a)* manufacturing a biological microchip comprising an ordered array of three-dimensional hydrogel elements on a solid support, obtained by a method of photo- or chemically induced polymerization and containing immobilized antibodies, wherein an antibody is immobilized in each separate cell; *b)* incubating the microchip in a reaction medium which comprises a sample to be analyzed, for forming immune analyte-antibody complexes, which incubation, when necessary, is carried out under stirring conditions; *c)* detecting the formed complex; and *d)* quantitative detection of the analyte as taught by Wagner et al., and incorporate the detection of biological toxins as taught by Ewalt et al., in order to incorporate detecting toxins and biotoxins using microchip technology as part of a platform for detecting warfare agents. One of ordinary skill in the art would have a reasonable expectation of success by incorporating biological toxins into the method for quantitative detection comprising: a biological microchip wherein no more then routine skill would have been required to exchange the analyte for the biological toxin, especially since both Wagner et al., and Ewalt et al., teach the manufacturing or

purchasing biological microchips, immobilizing antibodies in separate cells; an incubation step, formation of immune analyte-antibody complexes, and quantitative detection of the analyte; only using the well known claimed elements with no change in their respective function wherein the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Finally it would have been prima facie obvious to combine the invention of Wagner et al., and Ewalt et al., to advantageously assay large numbers of samples in a matter of minutes because microchip technology works with immunoassays and in combination with mass spectrometry and fluorescent detection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubina et al., (BioTechniques. 2003. Vol. 34(5):1008-1022) in view of Ligler et al. (2003. Anal. Bioanal. Chem. Vol. 377:469-477).

The claims are drawn to method for quantitative detection of biotoxins in a sample, comprising the steps of: *a)* manufacturing a biological microchip comprising .an ordered array of three-dimensional hydrogel elements on a solid support, obtained by a

method of photo- or chemically induced polymerization and containing immobilized antibodies to various bacterial, plant or animal toxins or biotoxins, wherein an antibody to an individual biotoxin or an individual biotoxin is immobilized in each separate cell; *b)* incubating the microchip in a reaction medium which comprises a sample containing biotoxins to be analyzed, for forming immune biotoxin-antibody complexes, which incubation, when necessary, is carried out under stirring conditions; *c)* detecting the formed complex; and *d)* quantitative detection of the biotoxin being analyzed. Claim 2 is drawn to the immobilized antibodies comprising antibodies selected from the group of antibodies to ricin, viscumin, staphylococcal enterotoxin B, tetanus toxin, diphtheria toxin, lethal factor of anthrax toxin. Claim 3 is drawn to the immobilized biotoxins comprising biotoxins selected from the group comprising ricin, viscumin, staphylococcal enterotoxin B, tetanus toxin, diphtheria toxin, lethal factor of anthrax toxin. Claim 4 is drawn to detecting the complex formed in step *c)* and subsequent quantitative detection in step *d) are* carried out in a format of direct immunoassay.

Claim 5 is drawn to the reaction medium in step; *b)* additionally contains antibodies to a biotoxin, and the detection of the complex formed between the biotoxin immobilized on the chip and the antibody against this biotoxin in step; *c)* and subsequent quantitative detection in step *d) are* carried out in the format of competitive immunoassay. Claim 6 is drawn to the reaction medium in step *b)* further contains a labeled biotoxin, and detection of the complex formed between the antibody immobilized on the chip and the biotoxin in step *c)* and subsequent quantitative detection in step *d) are* carried out in the format of competitive immunoassay. Claim 7

is drawn to detection of the complex formed in step *c)* and subsequent quantitative detection in step *d) are* carried out in the format of sandwich-immunoassay. Claim 8 is drawn to the quantitative detection of the biotoxin is effected by carrying out steps *a)--c)* with known concentrations of the biotoxin being analyzed and with plotting a calibration dependence curve, from which the amount of the biotoxin being analyzed in the sample is determined. Claim 9 is drawn to the step *c)* wherein detection of the formed complex is carried out fluorimetrically, chemiluminometrically or mass-spectrometrically.

Rubina et al., teach hydrogel-based protein microchips: manufacturing, properties and applications. Rubina et al., teach 3-D hydrogel chips are advantageous over 2-D because of the high immobilization capacity simultaneously with distant spacing of immobilized molecules and the gel allows accessibility from all sides, prevents protein-protein contact, and results in a high sensitivity of on-chip analysis (page 1008). Rubina et al., teach manufacturing immobilized microarrays of gel elements chips with different proteins and ligands (page 1008). The main step is photo-induced copolymerization of acrylamide gel monomers with proteins, oilgonucleotides, or low molecular ligands wherein the applications for these protein chips allow for qualitative and quantitative analysis (page 1008-09). Rubina et al., teach labeling proteins with fluorescent dyes (page 1010). Rubina et al., teach microchip analysis with fluorescence and chemiluminescence measurements and Matrix-assisted laser desorption/ionization- time of flight mass spectrometric analysis (page 1010). Rubina et al., teach fluorescently labeled proteins applied to the microchips with immobilized

proteins incubated at a constant temperature and fluorescent measurements with taken (page 1011).

Rubina et al., teach an immunoassay with immobilized monoclonal antibodies, labeled secondary antibodies and fluorescent signals were plotted versus known protein concentrations to measure the protein in the samples (page 1011). Rubina et al., teach the calibration curve was obtained by plotting fluorescent signals against concentrations in the chip immobilized control lysates (page 1011). Rubina et al., teach antibody-antigen interactions on microchips detected by fluorometric, mass-spectrometric and chemiluminescent means (page 1016). Rubina et al., teach sandwich immunoassays (page 1016). Rubina et al., teach the protein chips show negligible fluorescence background, low nonspecific binding and can be used repeatedly (page 1020). Rubina teach quantitative analysis can be carried out in complex mixtures (page 1020). However Rubina et al., do not specifically recite the detection of biotoxins.

Ligler et al., teach array biosensors for the detection of toxins in order to expedite appropriate countermeasures. Ligler et al., teach the desire to test for exposure to toxins in environmental samples, pollutants, toxic compounds as a result of terrorist activity and in the food supplies (page 469, col. 2). Ligler et al., teach a simple easy to use multi-analyte detection and measurement biosensor where capture molecules are immobilized on the surface; solutions and reagents are loaded onto the modules allowing binding of the multiple analytes to their specific capture molecules and parallel analysis occurs (page 470, col. 2). Ligler et al., teach both sandwich and competitive immunoassays have been used for detection of analytes wherein the identity of the

toxin the sample is determined by the location of the spot that increases in the sandwich assay or the decrease in a competitive assay in fluorescence intensity (page 470, col.2). Ligler et al. teach in the methods section entitled Antibodies and Toxins disclose commercially available staphylococcal enterotoxin B and ricin along with labeled antibodies and toxins (page 470-471). Ligler et al, teach the immobilization of capture antibodies, labeled antibodies and labeled proteins (page 471, col. 1). Ligler et al., teach two methods for the competitive immunoassay (page 471, col.2). The labeled capture antibody was immobilized on the surface, unlabeled compound competed with the labeled analyte for binding to the immobilized capture antibody to thereby allow the percent inhibition to be calculated (page 471, col.2). Ligler et al., also teach a competitive assay where biotinylated fumonisin biotoxin was immobilized on the surface, test sample containing anti-fumonsisin and various concentration of fumonisin B1 were introduced and competed with the immobilized fumonisin for binding to the fluorescent antibodies (page 471, col. 2). Figure 4 shows dose response curves for detection of toxins using rapid sandwich immunoassay format. Ligler et al., teach the array biosensor as a rapid, fieldable, user-friendly instrument capable of testing multiple complex samples in parallel for multiple toxic agents (page 476, col. 1).

Therefore it would have been prima facie obvious at the time of applicants invention to modify the method for quantitative detection comprising: *a)* manufacturing a biological microchip comprising an ordered array of three-dimensional hydrogel elements on a solid support, obtained by a method of photo- or chemically induced polymerization and containing immobilized antibodies, wherein an antibody is

immobilized in each separate cell; *b)* incubating the microchip in a reaction medium which comprises a sample to be analyzed, for forming immune analyte-antibody complexes, which incubation, when necessary, is carried out under stirring conditions; *c)* detecting the formed complex; and *d)* quantitative detection of the analyte as taught by Rubina et al., to incorporate detecting toxins and biotoxins as taught by Ligler et al., in order to determine exposure to biotoxins and toxins as taught by Ligler et al. One of ordinary skill in the art would have a reasonable expectation of success by incorporating toxin and biotoxin analytes into the method for quantitative detection comprising: a biological microchip wherein no more then routine skill would have been required to exchange the generic pathogen analyte for the biotoxin analyte, especially since both Rubina et al., and Ligler et al., teach *the same method steps including* manufacturing a biological microchips, obtained by polymerization and containing immobilized antibodies in separate cells; an incubation step, formation of immune analyte-antibody complexes, detection the formed complex, and quantitative detection of the analyte; only to have the claimed elements which were well known in the prior art with no change in their respective function and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Finally it would have been prima facie obvious to combine the invention of Rubina et al., and Ligler et al., to advantageously achieve high immobilization capacity simultaneously with distant spacing of immobilized molecules accessibility from all sides, prevents protein-protein contact, and results in a high sensitivity of on-chip analysis using hydrogel within a

rapid, fieldable, user-friendly instrument capable of testing multiple complex samples for multiple toxic agents.

Conclusion

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645